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Sarcopenia in rheumatoid arthritis: prevalence, influence of disease activity and associated factors

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Abstract Evaluate the prevalence of sarcopenia on patients with rheumatoid arthritis (RA), the influence of sarcopenia on disease activity and factors associated with sarcopenia. One hundred and twenty-three patients aged over 18 years with RA based on the 1987 ACR/EULAR classification criteria were enrolled. We performed a whole body DXA scan using a dual-energy X-ray absorptiometry (DXA) scanner lunar prodigy to measure fat mass, lean mass, and bone mass in the whole body and body parts. According to the anthropometric equation by Baumgartner et al., sarcopenia was defined as Relative skeletal mass index (RSMI) <5.5 kg/m^2 on women and <7.26 kg/m^2 on men. Body mass index (BMI) and waist circumference were measured and patients were classified according to World Health Organization. Disease activity was evaluated by: disease activity score 28 ESR (DAS28 ESR), disease activity score 28 CRP (DAS28 CRP), clinical disease activity index (CDAI), simplify disease activity index (SDAI). We measured functional disability by Health assessment questionnaire (HAQ). History and previous medication use including steroids were also checked, and comorbidities were recorded. We analyzed the relation between disease parameters and sarcopenia with the *r* of Pearson and Spearman. Factors associated and related to sarcopenia were assessed using multiple regression analysis and *t* independent test. We included 123 patients (107 women). 49 subjects (39.8%) where suffering from sarcopenia, of which 40 women. Most of the sarcopenic patients were between 41 and 50 years old. Sarcopenia on female subjects was not related to parameters of disease activity evaluated by DAS 28, CDAI and SDAI. Most of the sarcopenic patients had normal BMI and abnormal waist circumference. In simple regression analysis sarcopenia was related to BMI, DAS 28 ESR, bone erosion, waist circumference and HAQ. In multiple regression analysis, sarcopenia was positively related to an increase cardiometabolic risk [$p=0.025$, OR 0.176, CI (0.038–0.980)], normal BMI [$p=0.004$, OR 12.3, CI (2.27–67.6)], over fat BMI [$p=0.004$, OR 12.3, CI (2.27–67.6)] and bone erosion [$p=0.012$, OR 0.057 CI (0.006–0.532)]. No statistical difference was found according to disease duration and steroids use between sarcopenic and non sarcopenic patients. Sarcopenia is prevalent and related to age, bone erosion, normal/over fat BMI and high cardiometabolic risk according to waist circumference but not with disease activity.

Keywords Rheumatoid arthritis · Sarcopenia · Disease activity · Associated factors

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Introduction

Sarcopenia is a syndrome in which muscle mass loss is linked to functional loss. Many risk factors and mechanisms take part in sarcopenia's development. Among them, chronic inflammation which is particularly common in

rheumatoid arthritis (RA), a well defined chronic inflammatory disease.

Sarcopenia is known to induce decrease of muscle strength, an increase of risk of falls, neuromuscular weakness, balance disorders due to immobility [1], and risk of mortality [2]. In RA, there are many factors able to increase the risk of sarcopenia. Among them: decrease in physical activity [3], elevated tumor necrosis factor α (TNF-α) and interleukin 1 β (IL-1β) levels, increased energy expenditure during rest, high C-reactive protein (CRP) levels, immobility secondary to stiffness, and pain [4].

The consequences are important to consider especially with patients suffering from RA which comes along with several co morbidities-including cardio metabolic ones. Thus, it is important to prevent and detect sarcopenia in patients diagnosed with RA.

Some authors have shown that unhealthy body composition (BC)—especially rheumatoid cachexia, sarcopenic obesity—were related to disease activity, disability scores, rheumatoid factors (RF) [5–7]. However, the relationship and influence between sarcopenia and RA remain unstudied. Many studies evaluated body composition in RA patients and factors related to abnormal BC using BMI. During last years, DXA has been used to evaluate BC.

The purposes of this study were to evaluate the prevalence of sarcopenia, determinate the influence of sarcopenia on disease activity and the factors associated to sarcopenia in patients suffering from RA.

Materials and methods

Subjects

We included 123 patients aged over 18 diagnosed with RA according to the 1987 American College of Rheumatology/European League Against Rheumatism classification criteria. The patients were found at the Rheumatology department of El Ayachi Hospital between June and August 2014. The study was conducted with the approval of the ethics Committee of the faculty of medicine and pharmacy of Rabat. All the patients were informed about the objectives of the study and gave their consent. They were asked about disease duration and previous medication use, including steroids. Physical test was performed to search parameters of disease activity and complications of RA. All the patients underwent dual-energy X-ray absorptiometry (DXA).

Disease activity

The disease activity was evaluated by tender joint counts (TJC28), swollen joint counts (SJC28), patient global assessment of disease activity (PGA), evaluator global assessment of disease activity (EGA), disease activity score 28 erythrocyte sedimentation rate (DAS28 ESR) and C reactive protein (DAS 28 CRP), clinical disease activity index (CDAI) and simplify disease activity index (SDAI). In addition, C reactive protein (mg/l), rheumatoid factors (U/l) and anti-cyclic citrullinated peptides (anti-CCP) antibodies (U/l) were also recorded. Physical test was performed to search parameters of disease activity and complications of RA. All the patients underwent dual-energy X-ray absorptiometry (DXA).

Disability measure

Disability was measured by the Health Assessment Questionnaire (HAQ) disability index (HAQ-DI).

Anthropometric measures

Body mass index (BMI) was calculated as body weight [kg/height (m^2)] and patients were classified as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), and obese (>30) according to World Health Organization (WHO) [8]. Waist circumference was measured in centimeters (cm). We considered that a waist circumference over 80 cm for women and 94 cm for men was linked to an increased cardiometabolic risk, risk which became particularly significant when the waist circumference was over 88 cm for women and over 102 cm for men according to WHO and American Diabetes Association [9].

Definition of sarcopenia

Whole body DXA scan was performed using a DXA scanner lunar prodigy to measure fat mass, lean mass, and bone mass of the whole body (except head) and body parts. Appendicular skeletal muscle mass (ASM) was calculated as the sum of skeletal muscle mass in the arms and legs, assuming that all non-fat and non-bone tissue is skeletal muscle [10, 11]. Relative skeletal mass index (RSMI) was derived from the appendicular skeletal muscle mass in kilograms divided by the square of the height in meters [10, 12]. According to the anthropometric equation by Baumgartner et al. sarcopenia was defined as RSMI <5.5 kg/m^2 for women and <7.26 kg/m^2 for men [10]. Muscle performance was not assessed in our study.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 18.0. The correlation between individual and composite measures of disease activity and sarcopenia were analysed by

Spearman's and Pearson's tests. We also evaluated association between those parameters, BMI and sarcopenia using chi-square test. The relationship between sarcopenia and age, sex, disease duration, steroids long use was studied.

Linear regression analysis was performed between the parameters DAS-28, CDAI, SDAI, HAQ-DI and sarcopenia followed by multiple regression analysis to determine factors related to sarcopenia.

Results

We included 123 patients in this transversal study. Table 1 shows the characteristics of the patients. Average disease duration was 9.8 ± 8 years, and average DAS 28 ESR was 4.6 ± 1.5. Average HAQ-DI was 1.3 ± 0.7. Nine patients were in remission, nine in low disease activity, 58 in moderate and 47 in high disease activity.

Sarcopenia

Forty nine subjects (39.8%) from which 40 women were suffering from sarcopenia. Most of the sarcopenic patients were between 41 and 50 years old (13.8%), followed by patients under 40 years (10.6%). Sarcopenia was less prevalent on patients between 51 and 60 years old.

In Table 2, we compared age, disease duration, steroids use, DAS 28 ESR, HAQ, BMI, waist circumference and CRP between sarcopenic and non sarcopenic patients. There was no difference according to the onset of the disease, the disease duration, steroids use, disease activity estimated with DAS 2 ESR and HAQ between sarcopenic and non sarcopenic group. Non sarcopenic patients had statistically significant higher BMI, circumference waist, CRP and lower RSMI.

Patients under 40 years old presented a strong positive correlation between age and sarcopenia ($p < 0.001$, $r = 0.80$). Thirty-one (63.2%) from the patients with normal BMI were sarcopenic. In the sarcopenic group, 27 (55.1%) patients presented no cardiometabolic risk, 10 patients (20.4%) had increased risk, and 12 (24.5%) presented a substantially increased risk.

In simple regression analysis presented in Table 3, sarcopenia was related to overweight according to BMI, normal BMI, DAS 28 ESR, bone erosion, increased cardiometabolic risk, and HAQ.

In Table 4, we performed a multiple regression analysis which revealed that significant contributors to sarcopenia were: increased cardiometabolic risk, normal BMI, overweight and bone erosion.

Above, we mentioned that sarcopenic and non sarcopenic patients were not different according to DAS 28 ESR; since the definition of sarcopenia differs in men and women, we performed a subgroup analysis in Table 5 to compare the parameters of disease activity.

We compare DAS 28 ESR, SDAI and CDAI between sarcopenic and non sarcopenic womens in high or moderate disease activity. We did not found any statistically relevant difference (data are not shown).

Table 1 Characteristics of participants and disease

Parameters	Values
Female % (*n*)	87 (107)
Age in years[a]	52.3 ± 13.2
Disease duration in years[a]	9.8 ± 8
Drugs treatment[b]	
Cs DMARDs % (*n*)	90.2 (111)
Methotrexate	88.6 (109)
Salazopyrin	22 (27)
Antimalarial drug	6.5 (8)
Leflunomide	2.2 (3)
b DMARDs[b]	8.1 (10)
Steroids % (*n*)/daily dose range in mg[a]	85.4 (105)/11 ± 9
SDAI[a]	14.5 ± 12
CDAI[a]	18 ± 12.6
DAS28 ESR[a]	4.6 ± 1.5
Remission	7.31 (9)
Low disease activity	7.31 (9)
Moderate disease activity	47.15 (58)
High disease activity	38.21 (47)
DAS28 CRP[a]	4.05 ± 1.39
HAQ[a]	1.3 ± 0.7
BMI (kg/m^2)[a]	25.9 ± 5.84
RSMI (kg/m^2)[a]	6.18 ± 0.97
ESR mm/h[a]	41 ± 28.3
CRP mg/l[a]	22 ± 28
RF positive % (*n*)[b]	81.3 (100)
Anti-CCP positive % (*n*)[b]	83.7 (103)

SDAI simplify disease activity index, *CDAI* clinical disease activity index, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire, *BMI* body mass index, *RSMI* relative skeletal mass index ,*CRP* C-reactive protein, *RF* rheumatoid factor, *Anti CCP* anti cyclic citrullinated peptides, *Cs DMARDs* conventional synthetic disease-modifying antirheumatic drugs, *b DMARDs* biological DMARDs

[a]Mean and standard deviation

[b]Percentage and number

Discussion

This study shows that sarcopenia is frequent, as more than one RA patient on three were sarcopenic.

Ceyhan et al. [13] found a prevalence of sarcopenia of 43.3% while Giles et al. [14] reported a prevalence

Table 2 Comparison between sarcopenic and non sarcopenic patients

	Non sarcopenic patients ($n = 74$)	Sarcopenic patients ($n = 49$)	p value
Age (years)	54.2 ± 10.4	49.3 ± 19.3	0.044*
Age at the onset of the disease	43.7 ± 14.9	39.5 ± 16.3	0.138
Disease duration (years)	9.1 ± 7.6	10.8 ± 8.4	0.248
Steroids use (months)	68.5 ± 84	104.2 ± 194	0.198
DAS 28 ESR	4.5 ± 1.3	4.7 ± 1.7	0.432
DAS 28 CRP	3.9 ± 1.15	4.27 ± 1.68	0.145
SDAI	13.45 ± 11.36	16.06 ± 12.76	0.238
HAQ	1.3 ± 0.6	1.4 ± 0.8	0.401
BMI (kg/m^2)	28.8 ± 5	21.5 ± 3.9	<0.001*
RSMI (kg/m^2)	6.65 ± 0.72	5.46 ± 0.85	<0.001*
Circumference waist (cm)	99.7 ± 12.6	84.3 ± 12	<0.001*
ESR	38.55 ± 26.47	44.9 ± 30.76	0.228
CRP[a]	8 (5.18)	14 (0.95)	0.036*
RF positive	228 ± 234	235.68 ± 228	0.873
Anti-CCP positive	246 ± 287	367 ± 418	0.084

DAS disease activity score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SDAI* simplify disease activity index, *CDAI* clinical disease activity index, *HAQ* Health Assessment Questionnaire, *BMI* body mass index, *RSMI* relative skeletal mass index, *RF* rheumatoid factor, *Anti CCP* anti cyclic citrullinated peptides

*p value < 0.05

[a]Median value, p evaluated by U Mann Whitney test

Table 3 Simple regression analysis on sarcopenia

	OR	CI	p value
Increased cardiometabolic risk	0.309	0.102–0.936	0.038*
Normal BMI	221	18.432–2649	<0.001*
Over fat	17.5	3.8–79	<0.001*
DAS 28 ESR	0.433	0.194–0.967	0.041*
HAQ	0.396	0.139–0.979	0.045*
Bone erosion	0.28	0.102–0.936	0.040*

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire

*p value < 0.05

of 25.9%. They defined sarcopenia on the criteria proposed by Janssen et al. [15], as a relative skeletal muscle index ≤5.75 kg/m^2 for women and ≤8.50 kg/m^2 for men. The difference with our results can be explained by the difference in the definition of sarcopenia. Moreover, Ceyhan et al. included only female subjects in their study. CRP did not significantly contribute to sarcopenia in our study. However, like Ceyhan et al. we found that sarcopenic

Table 4 Multiple regression analysis on sarcopenia

	OR	CI	p value
Increase cardiometabolic risk	0.176	0.038–0.980	0.025*
Normal BMI	82.1	3.8–1733.3	0.005*
Over fat	12.3	2.27–67.6	0.004*
DAS 28 ESR	0.420	0.124–1.421	0.163
HAQ	0.415	0.101–1.71	0.223
Bone erosion	0.057	0.006–0.532	0.012*

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire

*p value <0.05

patients tend to have higher CRP value than non sarcopenic ones.

Many authors have shown the relationship between CRP and sarcopenia. Visser et al. [16] reported an association between muscle strength, mass measurements and blood TNF-α, interleukin 6 (IL-6), and CRP levels. High levels of IL-6 and CRP are related to loss in muscle strength. These cytokines increase proteolysis during muscle tissue synthesis.

Schaap et al. [17], Cesari et al. [18] also found an association between high CRP levels and sarcopenia; their study respectively included 986 and 286 subjects who were not suffering from RA.

We found a relationship between ESR, DAS 28 ESR, SDAI, CDAI and sarcopenia on men, but not on women. This difference might be explained by the fact that RA on men was more severe according to DAS 28, SDAI and CDAI compared with RA on women. However, the small number of the patients does not allow any conclusion. No study has found a relationship between sarcopenia and disease activity according to DAS 28, CDAI or SDAI. Dao et al., El Maghraoui et al. have shown that body composition (BC) changes—rheumatoid cachexia and overweight—were associated with high DAS 28 score [5, 6].

Sarcopenia was positively correlated to "normal" and "overweight" according to BMI. Ceyhan et al. [13], Giles et al. [14] found that sarcopenia was more prevalent in the RA group than controls and even more common among normal and overweight subset than obese subset.

It is well established that RA increases the risk of cardiovascular (CV) mortality by up to 50% compared with the general population [19, 20] and CV disease (CVD) is the leading cause of death in RA patients [19–21]. Chin et al. [22], Sanada et al. [23] have shown relationship between sarcopenia and high cardiovascular risk in general population through several mechanisms: increase of fat mass, decrease of muscle (following functional impairment and physical disability) and myokine production (cytokines

Table 5 Comparison between steroids use, disease activity in relation to the presence of sarcopenia in men and women

Parameters	Women ($n = 107$)			Men ($n = 16$)		
	Sarcopenic ($n = 40$)	Non sarcopenic ($n = 67$)	p	Sarcopenic ($n = 9$)	Non sarcopenic ($n = 7$)	p
Steroid use (months)	119	72.3	0.16	30	22	0.76
DAS 28 ESR	4.6 ± 1.8	4.7 ± 1.2	0.74	5.5 ± 0.8	3 ± 1.8	0.03*
DAS 28 CRP	4 ± 1.8	4 ± 1.1	0.67	5 ± 0.3	3.1 ± 1.4	0.02*
SDAI	15.2 ± 13	14 ± 11	0.45	19.7 ± 2.6	8.7	0.06*
CDAI	19 ± 15	17.4 ± 11	0.60	23 ± 4	12.7 ± 11	0.016*
ESR (mm/h)	41 ± 27	41 ± 26	0.92	59.4 ± 40	14.5 ± 12	0.013*

DAS disease activity score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SDAI* simplify disease activity index, *CDAI* clinical disease activity index

*p value < 0.05

with anti-inflammatory effect) [24, 25]. We can then suppose that a patient with both RA and sarcopenia has a more substantial increase CV risk than for a non sarcopenic one. It is well known that obesity (BMI) is strongly associated with an increased risk of overall mortality and cardiovascular mortality; but in their study, Maradit et al. [26], Escalante et al. [27] recently reported paradoxical protective effects of increasing BMI on cardiovascular and all cause mortality.

The effects of sarcopenia on CV outcomes may be shifted into normal and overweight with RA patients; thus RA and sarcopenic patients with low BMI are more exposed than those with normal and overweight BMI.

Along with sarcopenia, other BC's abnormalities may increase CV risk. Rheumatoid cachexia (which includes sarcopenia), sarcopenic obesity may promote cardiovascular risk, morbidity and mortality [28]. Lean mass is associated with a decreased level of exercise due to sarcopenia and may lead to increased insulin resistance and CVD comorbidity with RA patients [29].

We found that increased cardiometabolic risk according to waist circumference was positively correlated to sarcopenia which can be explained by the increase of fat mass on sarcopenic patients. We did not find another study which has already addressed this topic.

Bone erosion was positively related to sarcopenia; in Giles et al. 14], abnormal BC was significantly associated with joint deformity.

Like Ceyhan et al. and Giles et al. [13, 14], we did not find any link between steroids use, DMARDs intake and sarcopenia development in this study.

Our study has some limits. Indeed, we had no control group, we did not assess muscle performance and the number of men in our sample was too small to allow any conclusion.

To conclude, we showed that sarcopenia is frequent on RA patients, mostly on those classified as normal or overweight according to BMI, showing that BMI does not reflect sarcopenia or real body composition compared to DEXA. RA patients with sarcopenia had an increased cardiometabolic risk which is added to high cardiovascular risk already associated with the disease. High CRP is a contributive factor to sarcopenia but disease activity does not influence sarcopenia, as well as steroids use or DMARDs intake in our study. Detecting sarcopenia in RA is important to prevent the consequences of this comorbidity which includes CV risk disease and mortality.

The perspectives in further studies would be to specify the role of sarcopenia in RA—especially on CV risk—and evaluate the factors influencing sarcopenia on a large sample of men with RA to compare these results with those observed on women. It is important to establish clear recommendations to manage sarcopenia especially on young patients whose quality of life is altered by this condition.

Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

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